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EXAMINER
YOUNG, JOSEPHINE

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/17/2003 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/853,047	Applicant(s) SAMPATH ET AL.	
	Examiner Josephine Young	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003 and 10 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *10-12 and 21-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13-20* is/are rejected.

7)☒ Claim(s) *14-20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5,9* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 8, mailed February 10, 2003, is acknowledged. The traversal is on the ground(s) that the subject matter of Groups I, V and VI are so closely related that the search for the subject matter of one of the Groups would lead to the subject matter of the other Groups; therefore, there is not a significant search burden. This is not found persuasive because these inventions are distinct and have acquired a separate status in the art as shown by their different classification and their recognized divergent subject matter. A search for the polymeric compounds of Group I would not be coextensive with the pyrimidine nucleoside derivatives of Group V or the deoxyribose sugar derivatives of Group VI as indicated by their different classifications. The divergent nature of the compounds based upon the different structural core necessitates restriction in the instant case. A reference directed to polymeric compound could not reasonably be expected to be a reference directed to a single nucleoside residue or a sugar analog. Searching the three inventions constitutes a burdensome search, as a thorough search comprises a search of foreign patents and non-patent literature, as well as the appropriate U.S. patent classifications. To search the three independent and distinct inventions would indeed impose an undue burden upon the examiner in charge of this application.

Because these inventions are distinct and have acquired a separate status in the art as shown by their different classification and because of their recognized divergent subject matter, restriction for examination purposes is still deemed proper and is therefore made FINAL.

Accordingly, claims 10-12 and 21-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's election of Species Group B in Paper No. 11, transmitted April 10, 2003, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement with regard to the election of species, the election of species has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

Claims 14-20 are objected to because of the following informalities: Claim 14 contains two periods.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 13-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "nucleoside analogs" in claims 1 and 14 renders the claims in which it appears indefinite. In the absence of the specific modification to the nucleoside or distinct language to

describe the structural modifications or the chemical names of the modified nucleoside of this invention, the identity of said nucleoside analogs would be difficult to describe and the metes and bounds of said nucleoside analogs that Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

The term "pharmaceutically active" in claims 1 and 14 renders the claims in which it appears indefinite. The term "pharmaceutically active" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, in claim 2, one of the listed pharmaceutically active nucleosides is adenosine. Therefore, it is unclear as to if Applicant intends for the claims to encompass heteropolymeric compounds that simply include a chain of naturally occurring nucleosides.

Claim 5 recites the limitation "nucleobases"; however, there is insufficient antecedent basis for this limitation in the claim.

The terms "nucleoside" and "nucleoside analogs" with respect to the definition of R^1 in claim 14 renders the claims in which it appears indefinite. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The terms "nucleoside" and "nucleoside analogs" with respect to the definition of R^1 in claim 14 is used by the claim to mean "purine or pyrimidine base" (see

claim 15), while the accepted meaning of the terms "nucleoside" and "nucleoside analogs" includes not only the base but also a pentose. See also page 10 of the specification. The term is indefinite because the specification does not clearly redefine the term.

The term "optionally present" with respect to the definition of R^1 in claim 14 renders the claims in which it appears indefinite. It is unclear as to if optionally present indicates that R^1 is hydrogen, or if the carbon to which R^1 is bound is left with an open valence, i.e. is a trivalent carbon.

The term "O^-" with respect to the definition of R^4 in claim 14 renders the claims in which it appears indefinite. It is unclear as to if Applicant intends to claim simply the anion, or if Applicant intends to claim a negatively charged polymer species with a positively charged counter ion. Further, it is unclear as to what that counter ion would be if present.

The term "NH_2" with respect to the definition of R^3 in claim 15 renders the claims in which it appears indefinite. It is unclear as to if Applicant intends for R^3 to be a tetravalent nitrogen, i.e. a charged species, or if Applicant actually intends R^3 to be NH, a trivalent nitrogen.

The terms "C=O" and "C=S" with respect to the definition of R^6 in claim 15 renders the claims in which it appears indefinite. It is unclear as to if Applicant actually intends for R^6 to be a trivalent carbon, i.e. a charged species.

Claim 15 is indefinite because it is unclear as to if all the R^1 in the compound are restricted to the recited limitations, or if only one of the R^1 in the compound are so limited, since claim 14 independently defines each R^1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-9, 13-17 and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by the international publication WO 94/17093 to HYBRIDON, INC. (citation no. 3 in paper no. 4, IDS Form 1449, filed October 26, 2001).

HYBRIDON teaches various oligonucleotide analogs with at least one ribonucleotide alkylphosphonate or alkylphosphonothioate, which preferably also contains at least one ribonucleotide substituted at the 2'-postion of the ribose group. See Abstract. On page 4, lines 1-5, HYBRIDON discloses that the oligonucleotides include molecules having modified nucleic acid/bases and/or sugars, added substituents, and 2'-substituted ribonucleoside monomers. On page 8, lines 6-18, HYBRIDON discloses various moieties that can be used in the 2'-position of the ribose group. In that same paragraph, HYBRIDON teaches that such 2'-substituted ribonucleosides help enhance duplex stability. Further, on page 7, lines 23-25, HYBRIDON discloses that such modifications to the nucleic acid sugar backbone improve cellular uptake and resistance to nuclease action. Each nucleotide residue is considered pharmaceutically active, in that in can form a stable duplex with the nucleic acid of a virus, pathogen, or gene, thereby inactivating it. See page 5, line 30 to page 6, line 1. Such compounds can be used to treat viral infection, infections by pathogenic organisms, or disease resulting from abnormal gene expression or from the expression of an abnormal gene product (page 5, lines 10-17). Further, in

that same paragraph, HYBRIDON teaches that the compounds can be formulated with a physiologically acceptable carrier.

Claims 1-3, 6 and 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by the article GIANNARIS *et al.*, Can. J. Chem., **1994**, *72* (3), 909-918 (citation no. 28 in paper no. 5, IDS Form 1449, filed October 19, 2001).

GIANNARIS teaches various oligoarabinonucleotides (arabinonucleic acids or ANA) that can hybridize to complementary DNA and RNA, i.e. oligonucleotides containing the sugar D-arabinose as antisense agents. See Abstract. Further, GIANNARIS discloses in the first paragraph, left column, page 909, that oligomers incorporating modified nucleoside units, including α-nucleosides, L-deoxyribo and L-ribonucleosides, glyceronucleosides, 4'-thionucleosides, carbocyclic nucleosides and 2'-O-alkyl nucleosides have also been explored as possible antisense agents with increased nuclease resistance. Each nucleotide residue is considered pharmaceutically active, in that in can form a stable duplex with a gene to regulate its function.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9 and 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over the patent US 5,457,187 to GMEINER et al. (citation no. 4 in paper no. 5, IDS Form 1449, filed October 19, 2001) and HYBRIDON.

Applicant claims heteropolymeric compounds with a chain of pharmaceutically active nucleosides and nucleoside analogs.

GMEINER teaches homo-oligonucleotides of between 2 and 26 monomers of 5-fluorouridine (5-FU) and 5-fluorodeoxyuridine (5-FdU) that exhibit antitumor activity. See Abstract. GMEINER discloses in column 2, lines 22-26, that the homo-oligomeric 5-fluorouridines and 5-fluorodeoxyuridines are used as a polymeric drug delivery system for production of 5-fluorodeoxyuridine monophosphate (FdUMP) and 5-fluorodeoxyuridine monophosphate (FdUMP), respectively, potent inhibitors of thymidylate synthetase (TS), an important target in cancer chemotherapy. In column 2, lines 53-56, GMEINER teaches that the delivery of homo-oligomeric 5-fluorouridines (FrU_n) results in degradation by nuclease to FUMP. Further, in column 3, lines 20-26, GMEINER teaches that enzymatic degradation of the homo-oligomeric nucleotides by 3'-exonucleases releases the nucleoside 5'-O-monophosphate (NMP), a metabolically activated product, which can be easily converted into a fully

metabolically activated product. The oligonucleotide compounds are also actively taken up by cells resulting in a higher intracellular concentration than for their monomeric counterparts. See column 3, lines 15-19. Therefore, the homo-oligomeric nucleotides provide higher therapeutic indices, reduce the dose required for a positive biological response and reduce dose-dependent toxic side effects. "The delivery of nucleosides and nucleoside analogues that have anti-cancer and anti-viral activity as monomers in the form of homo-oligomeric nucleotides ... has significant advantages relative to their delivery as monomers" (column 3, line 64 to column 4, line 2). In column 4, lines 3-11, GMEINER teaches other nucleoside analogs that are "equivalent substitutions" for 5-FU, and thus can be delivered in an equivalent way, i.e. via the polymeric drug delivery system.

GMEINER does not explicitly teach hetero-oligomeric nucleotides.

As set forth supra, HYBRIDON teaches various oligonucleotide analogs with at least one ribonucleotide alkylphosphonate or alkylphosphonothioate, which preferably also contains at least one ribonucleotide substituted at the 2'-postion of the ribose group. See Abstract. On page 4, lines 1-5, HYBRIDON discloses that the oligonucleotides include molecules having modified nucleic acid/bases and/or sugars, added substituents, and 2'-substituted ribonucleoside monomers. On page 8, lines 6-18, HYBRIDON discloses various moieties that can be used in the 2'-position of the ribose group. In that same paragraph, HYBRIDON teaches that such 2'-substituted ribonucleosides help enhance duplex stability. Further, on page 7, lines 23-25, HYBRIDON discloses that such modifications to the nucleic acid sugar backbone improve cellular uptake and resistance to nuclease action. Each nucleotide residue is considered pharmaceutically active, in that in can form a stable duplex with the nucleic acid of a virus,

pathogen, or gene, thereby inactivating it. See page 5, line 30 to page 6, line 1. Such compounds can be used to treat viral infection, infections by pathogenic organisms, or disease resulting from abnormal gene expression or from the expression of an abnormal gene product (page 5, lines 10-17). Further, in that same paragraph, HYBRIDON teaches that the compounds can be formulated with a physiologically acceptable carrier.

It would have been obvious to one of ordinary skill in the art to incorporate ribonucleotide alkylphosphonate or alkylphosphonothioate, which preferably also contains at least one ribonucleotide substituted at the 2'-postion of the ribose group, into the homopolymeric compounds of GMEINER, as such modifications to the nucleic acid sugar backbone improve cellular uptake and resistance to nuclease action. While the synthesis and cost of the polymeric compound would be effected by adding a different nucleoside to the chain, a skilled artisan would have been motivated and have had a reasonable expectation of success to make and use such heteropolymeric compositions to further improve the bioavailability and reduce the cytotoxicity of the monomeric nucleosides by controlling the rate of release of the monomeric nucleosides via nuclease degradation of the polymer, i.e. modifying the nucleic acid sugar backbone of the homopolymeric compound, as per HYBRIDON, to improve cellular uptake and resistance to nuclease action. Various nucleoside analogs are known to have anti-viral, ant-cancers or anti-microbial activity. Thus, the particular nucleoside analog known to be pharmaceutically effective used in the polymeric compound is seen as a choice of experimental design, and well within the purview of the prior art.

Claims 1-9 and 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article CHAPEKAR, et al., Biochemical and Biophysical Research Communications, 1983, 115 (1), 137-143 (citation no. 30 in paper no. 5, IDS Form 1449, filed October 19, 2001) and HYBRIDON.

CHAPEKAR teaches the cordyceptin trimer analog of $(A2'p)_2A$, namely $(3'\text{-}dA2'p)_23'dA$, which has activity against the human colon carcinoma cell line HT-29 *in vitro*. See Abstract. CHAPEKAR further discloses in the abstract that the trimers are hydrolyzed to the dimmer and monomer, namely 2'-deoxycoformycin, an adenosine deaminase inhibitor. "[T]he cordyceptin trimer core analog of 2',5'-oligoadenylate serves as a prodrug of cordyceptin under tissue culture conditions" (page 142, first full paragraph). In the first full paragraph on page 142, CHAPEKAR teaches that trimer analog was hydrolyzed to the dimmer and monomer species by the esterases. Finally, CHAPEKAR discloses that $(3'\text{-}dA2'p)_23'dA$ is an oligonucleotide prodrug and may serve as a sustained release form of cordyceptin to provide a longer maintained antitumor activity *in vivo*. See first full paragraph, page 143.

CHAPEKAR does not explicitly teach hetero-oligomeric nucleotides. Further, CHAPEKAR does not specifically state that other nucleoside analogs can be delivered in an equivalent way, i.e. via the polymeric drug delivery system.

As set forth supra, HYBRIDON teaches various oligonucleotide analogs with at least one ribonucleotide alkylphosphonate or alkylphosphonothioate, which preferably also contains at least one ribonucleotide substituted at the 2'-postion of the ribose group. See Abstract. On page 4, lines 1-5, HYBRIDON discloses that the oligonucleotides include molecules having modified nucleic acid/bases and/or sugars, added substituents, and 2'-substituted ribonucleoside

monomers. On page 8, lines 6-18, HYBRIDON discloses various moieties that can be used in the 2'-position of the ribose group. In that same paragraph, HYBRIDON teaches that such 2'-substituted ribonucleosides help enhance duplex stability. Further, on page 7, lines 23-25, HYBRIDON discloses that such modifications to the nucleic acid sugar backbone improve cellular uptake and resistance to nuclease action. Each nucleotide residue is considered pharmaceutically active, in that in can form a stable duplex with the nucleic acid of a virus, pathogen, or gene, thereby inactivating it. See page 5, line 30 to page 6, line 1. Such compounds can be used to treat viral infection, infections by pathogenic organisms, or disease resulting from abnormal gene expression or from the expression of an abnormal gene product (page 5, lines 10-17). Further, in that same paragraph, HYBRIDON teaches that the compounds can be formulated with a physiologically acceptable carrier.

It would have been obvious to one of ordinary skill in the art to incorporate ribonucleotide alkylphosphonate or alkylphosphonothioate, which preferably also contains at least one ribonucleotide substituted at the 2'-postion of the ribose group, into the homopolymeric compounds of CHAPEKAR, as such modifications to the nucleic acid sugar backbone improve cellular uptake and resistance to nuclease action. A skilled artisan would have been motivated and have had a reasonable expectation of success to make and use such heteropolymeric compositions to further improve the bioavailability and reduce the cytotoxicity of the monomeric nucleosides by controlling the rate of sustained release of the monomeric nucleosides via nuclease degradation of the polymer, i.e. modifying the nucleic acid sugar backbone of the homopolymeric compound, as per HYBRIDON, to improve cellular uptake and resistance to nuclease action. Various nucleoside analogs are known to have anti-viral, ant-cancers or anti-

microbial activity. Thus, the particular nucleoside analog known to be pharmaceutically effective used in the polymeric compound is seen as a choice of experimental design, and well within the purview of the prior art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Claims 1-31 are pending. Claims 1-9 and 13-20 are rejected. Claims 14-20 are objected to. Claims 10-12 and 21-31 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
June 13, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600